Remarks

Claims 24-35 are pending in this application. Claims 24, 29 and 31 are amended to recite "pregelatinized corn starch." Support for the amendments can be found, for example, on page 5, lines 5-11, page 11, lines 12-18, and page 16, Table 2 of the specification. No new matter has been added.

As discussed below, the claim amendments are made to put the claims in condition for allowance, as suggested by the Examiner. Applicants respectfully submit that all of the pending claims are allowable for the following reasons.

A. The Objection to Claims Under 35 U.S.C. § 132(a) Should Be Withdrawn

On page 2 of the Office Action, the claim amendments made in Applicants' previous response are objected to under 35 U.S.C. § 132(a) for allegedly introducing a new matter. In particular, it is alleged that the term "direct blend" is not "defined or even disclosed in the specification." (Office Action, page 2).

Although Applicants respectfully disagree, especially in view of the fact that a detailed exemplary process for making the compositions of this invention is described on page 13 of the specification[1], the claims are amended to recite, in part, a composition comprising a uniform admixture of thalidomide and pregelatinized corn starch, as suggested by the Examiners during the interview. In view of these amendments, Applicants respectfully request that the rejection of the claims under 35 U.S.C. §132(a) be withdrawn.

2. The Rejection of the Claims Under 35 U.S.C. § 103 Should Be Withdrawn

On pages 3-5 of the Office Action, claim 24 is rejected as allegedly obvious over U.S. Patent No. 5,643,915 to Andrulis, Jr. *et al.* ("Andrulis") and Gennaro, *Remington: The Science and Pharmacy*, pp. 1642-1649 (1995) ("Gennaro"). In particular, it is alleged that, while the arguments made in Applicants' previous response are recognized, "the claim is broad and reads on all carriers," including, according to the Examiner, those disclosed in the cited references.[2] (Office Action, pages 3-4). It is suggested that amending the claim to recite specific types of carriers would be beneficial. (*Id.*, page 3).

---

[1] It should be noted that sections 4.2.1-4.2.5, with the exception of section 4.2.3, describe the direct blend process which does not involve roller compaction. Although section 4.2.3 describes the roller compaction process, it is clearly provided that the roller compaction is an optional process ("the pre-blend may be passed through a roller compactor").

[2] It appears that a rejection under 35 U.S.C. § 112 is also present in the Office Action. In particular, it is alleged that claim 24 is not supported because the 50 mg capsule provided in the specification is a "prior art formulation." (Office Action, page 4). Applicants note that the Examiner is referring to Example 3 of the specification, which indeed is a prior art formulation. However, the claimed

Applicants respectfully disagree. This is because the references cited by the Examiner do not disclose or suggest a formulation containing the specific amount of carrier in the specific capsule size, as recited by claim 24 as presented in Applicants' previous response. (*See* Applicants' Response of December 7, 2005, pages 7-8), much less provide reasonable expectation of success. In addition, it was unexpected that the claimed composition, which contains much less carrier than thalidomide formulation commercially available at the time of this invention, is bio-equivalent to the commercially available formulation. (*Id.*, page 8).

Be that as it may, solely to expedite the prosecution of the present application, claim 24 is amended to recite, in part, a composition comprising 74 mg of pregelatinized corn starch, as suggested by the Examiner. In addition, as requested by the Examiner during the interview, Applicants submit herewith a copy of "Starch, Pregelatinized," *Handbook of Pharmaceutical Excipients*, 3rd Ed., pp. 528-530 (2000), which is a textbook widely used in the pharmaceutical art with regard to excipients. As the Examiner will see, "pregelatinzed starch" is well-defined and characterized, and no excessive variation exists as to the scope of the term. In view of these amendment and evidence, Applicants respectfully request that the rejection of claim 24 under 35 U.S.C. § 103 be withdrawn.

On pages 5-6 of the Office Action, claims 25-28 are rejected as allegedly obvious over Andrulis and Gennaro, further in view of U.S. Patent No. 6,914,067 to Govindarajan *et al.* ("Govindarajan"). Apart from the Examiner's analysis of Govindarajan, it is suggested that making claim 25 into an independent claim would put claims 25-28 in possible condition for allowance. Applicants respectfully point out that the amended claim 24 is indeed equivalent to claim 25 written in an independent form. Therefore, Applicants respectfully request that the rejection of claims 25-28 be also withdrawn.

On pages 6-7 of the Office Action, claims 29-30 are rejected as allegedly obvious over Andrulis and Gennaro, further in view of Baker *et al.*, Abstract 54, Hematology Society of Australia and New Zealand (2000) ("Baker"), Teo *et al.*, *J. Clin. Pharmacol.*, 39: 1162-1168 (1999) ("Teo I"), and Teo *et al.*, *Biopharmaceutics & Drug Disposition*, 21: 33-40 (2000) ("Teo II"). Applicants respectfully disagree.

Applicants respectfully submit that one cannot arbitrarily adjust the amount of carriers and expect the resulting formulation to have properties comparable to the

---

formulation is expressly described elsewhere in the specification that is other than in Example 3. (*See* Specification, page 5, lines 5-11). Therefore, it is clear that claim 24 is adequately supported by the specification.

original formulation. In response, the Examiner alleges that "[t]he Applicant is proving in their argument any carrier cannot be used but is claiming any carriers clearly contradicting themselves." (Office Action, page 7). However, Applicants respectfully point out that such an allegation is based on the misconstruction of Applicants' argument. Applicants clearly submitted that one cannot arbitrarily reduce the amount of a carrier with the expectation that the reduced amount of carrier would function equivalently with a higher amount of carrier. (*See* Applicants' Response of December 7, 2005, page 10).

Nevertheless, claim 29 is amended to recite, in part, a capsule formulation comprising "pregelatinized corn starch," as suggested by the Examiner. In view of this amendment, Applicants respectfully request that the rejection of claims 29-30 be withdrawn.[3]

On pages 7-8 of the Office Action, claim 31 is rejected as allegedly obvious over Andrulis and Gennaro, further in view of Scheffler *et al.*, *Clinical Pharmacology and Therapeutics*, 65(5): 483-490 (1999) ("Scheffler"). In particular, the Examiner alleges that, while Applicants "discussed pharmacokinetics" in their previous response, "the claim has no limit stating the pharmacokinetics," but "it only states a carrier." (Office Action, page 7). Applicants respectfully disagree.

Applicants respectfully point out that the "pharmacokinetics" of the claimed composition was discussed to show the unexpected characteristics exhibited by the claimed composition, all of the physical elements of which are recited by claim 31.[4] In other words, the "pharmacokinetics" referred to by the Examiner is an unexpected property of the composition defined or recited by claim 31. As such, Applicants respectfully point out that the "pharmacokinetics" of the claimed composition need not be recited by the claim, and thus respectfully request that the rejection of claim 31 be withdrawn.

Finally, the rejection of claims 32-35 is maintained in the Office Action based on the assertion that the claims are not allowable since claim 31, from which claims 32-35 depend, is not allowable. However, as discussed above, Applicants respectfully submit that claim 31 is indeed allowable. Consequently, Applicants respectfully request that the rejection of claims 32-35 be also withdrawn.

---

[3] Again, it is alleged that claim 29 lacks support because "the specification supports a 100 mg tablet, not a 100 mg capsule." (Office Action, page 7). Applicants note that the Examiner is referring to Example 2 of the specification. However, a 100 mg capsule of the invention is expressly disclosed elsewhere in the specification. (*See, e.g.*, Specification, page 11, Table 1). Therefore, Applicants respectfully point out that the allegation that claim 29 lacks support is without basis.

[4] In addition, claim 31, as it currently stands, recites a capsule formulation comprising "pregelatinized corn starch."

Conclusion

For at least the foregoing reasons, Applicants respectfully submit that all of the pending claims are allowable, and respectfully request that the rejection of the pending claims be withdrawn.

No fee is believed due for the submission of this paper. If any fees are required for the submission of this paper, or to avoid abandonment of this application, please charge such fees to Jones Day Deposit Account No. 503013.

Respectfully submitted,

Date: June 8, 2006

L0209
Hoon Choi (Ltd. Recog. No.)
JONES DAY
51 Louisiana Avenue, N.W.
Washington, DC 20001
(202) 879-3939

For: Anthony M. Insogna (Reg. No. 35,203)
JONES DAY
12750 High Bluff Drive - Suite 300
San Diego, CA 92130
(858) 314-1130

Handbook of PHARMACEUTICAL EXCIPIENTS

Third Edition

Edited by

Arthur H. Kibbe, Ph.D.

Professor and Chair
Department of Pharmaceutical Sciences
Wilkes University School of Pharmacy
Wilkes-Barre, Pennsylvania

American Pharmaceutical Association
Washington, D.C.

London, United Kingdom

Published by the American Pharmaceutical Association
2215 Constitution Avenue NW, Washington, DC 20037-2985, USA
www.aphanet.org
and the Pharmaceutical Press
1 Lambeth High Street, London SE1 7JN, UK
www.pharmpress.com

First edition 1986
Second edition 1994
Third edition 2000

Printed in the United States of America

ISBN: 0-85369-381-1 (UK)
ISBN: 0-917330-96-X (USA)

Library of Congress Cataloging-in-Publication Data
Handbook of pharmaceutical excipients / edited by Arthur H. Kibbe.--3rd ed.
p. ; cm.
Includes bibliographical references and index.
ISBN 0-917330-96-X
1. Excipients--Handbooks, manuals, etc. I. Kibbe, Arthur H. II. American Pharmaceutical Association.
[DNLM: 1. Excipients--Handbooks. QV 735 H236 2000]
RS201.E87 H36 2000
615'.19--dc21
99-044554

A catalogue record for this book is available from the British Library.

Managing Editor: Melanie Segala
Copyeditor: Paul Gottehrer
Indexer: Lillian Rodberg
Compositor: Roy Barnhill
Cover Designer: Tim Kaage

Starch, Pregelatinized

1. Nonproprietary Names

PhEur: Starch, pregelatinised
USP: Pregelatinized starch

2. Synonyms

Compressible starch; *Instastarch*; *Lycatab PGS*; *National 78-1551*; *Pharma-Gel*; *Prejel*; *Sepistab ST 200*; *Starch 1500*.

3. Chemical Name and CAS Registry Number

Pregelatinized starch [9005-25-8]

4. Empirical Formula Molecular Weight

$(C_6H_{10}O_5)_n$

Where n = 300-1000.

Pregelatinized starch is a starch that has been chemically and/or mechanically processed to rupture all or part of the starch granules and so render the starch flowable and directly compressible. Partially pregelatinized grades are also commercially available. Typically, pregelatinized starch contains 5% of free amylose, 15% of free amylopectin and 80% unmodified starch. The USP does not specify the botanical origin of the original starch but the PhEur specifies that corn (maize) starch should be used. *See also* Starch and Section 13.

5. Structural Formula

See Starch.

6. Functional Category

Tablet and capsule diluent; tablet and capsule disintegrant; tablet binder.

7. Applications in Pharmaceutical Formulation or Technology

Pregelatinized starch is a modified starch used in oral capsule and tablet formulations as a binder, diluent,[1] and disintegrant.[2]

In comparison to starch, grades of pregelatinized starch may be produced with enhanced flow and compression characteristics such that the pregelatinized material may be used as a tablet binder in dry-compression processes.[3-11] In such processes, pregelatinized starch is self-lubricating. However, when used with other excipients it may be necessary to add a lubricant to a formulation. Although magnesium stearate 0.25% w/w is commonly used for this purpose, concentrations greater than this may have adverse effects on tablet strength and dissolution. Therefore, stearic acid is generally the preferred lubricant with pregelatinized starch.[12]

Pregelatinized starch may also be used in wet granulation processes.[13]

Use	Concentration (%)
Diluent (hard gelatin capsules)	5-75
Tablet binder (direct compression)	5-20
Tablet binder (wet granulation)	5-10
Tablet disintegrant	5-10

8. Description

Pregelatinized starch occurs as a moderately coarse to fine, white to off-white colored powder. It is odorless and has a slight characteristic taste.

Examination of fully pregelatinized starch as a slurry in cold water, under a polarizing microscope, reveals no significant ungelatinized granules, i.e., no 'maltese crosses' characteristic of the starch birefringence pattern. Examination of samples suspended in glycerin show characteristic forms depending upon the method of drying used during manufacture, e.g., either irregular chunks from drum drying or thin plates. Partially pregelatinized starch (e.g., Starch 1500 and Sepistab ST 200) show retention of birefringence patterns typical of unmodified starch granules.

9. Pharmacopeial Specifications

Test	PhEur	USP
Identification	+	+
Botanic characteristics	+	—
pH (10% w/v slurry)	4.5-7.0	4.5-7.0
Iron	≤ 20 ppm	≤ 0.002%
Oxidizing substances	+	+
Sulfur dioxide	≤ 50 ppm	≤ 0.008%
Microbial limits	+	+
Loss on drying	≤ 15.0%	≤ 14.0%
Residue on ignition	—	≤ 0.5%
Foreign matter	+	—
Sulfated ash	≤ 0.6%	—
Protein	≤ 0.5%	—
Organic volatile impurities	—	+

10. Typical Properties

Acidity/alkalinity: pH = 4.5-7.0 for a 10% w/v aqueous dispersion.
Angle of repose: 40.7°[6]
Compressibility: *see* Starch, page 525
Density (bulk): 0.586 g/cm^3[a]
Density (tapped): 0.879 g/cm^3[a]
Density (true): 1.516 g/cm^3[a]
Flowability: 18-23% (Carr compressibility index)[14]
Moisture content: pregelatinized maize starch is hygroscopic.[11,15,16] *See also* Fig. 1.[a]
Particle size distribution: 30-150 μm, median diameter 52 μm. For partially pregelatinized starch, greater than 90% through a US #100 mesh (149 μm), and less than 0.5% retained on a US #40 mesh (420 μm).
Solubility: practically insoluble in organic solvents. Slightly soluble to soluble in cold water, depending upon the degree of pregelatinization. Fully pregelatinized starch conforms to the completeness of solution test in the USP. Pastes can be prepared by sifting the pregelatinized starch into stirred.

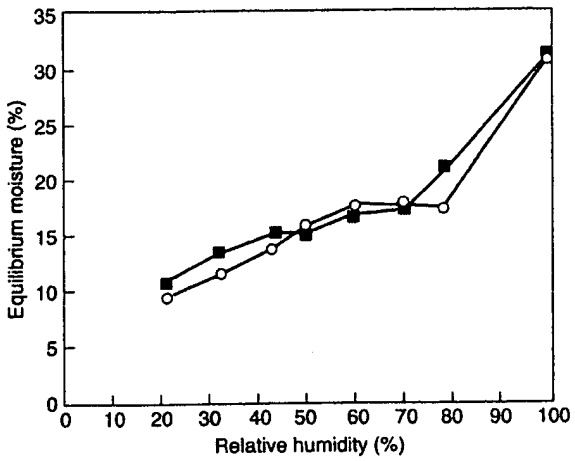

Fig. 1: Pregelatinized starch sorption-desorption isotherm.[a]
○ : Sorption
■ : Desorption

cold water. Cold water soluble matter for partially pregelatinized starch is 10-20%.

Specific surface area:
0.26 m^2/g (Colorcon);
0.18-0.28 m^2/g (Roquette Ltd).

Viscosity (dynamic): 8-10 mPa s (8-10 cP) for a 2% w/v aqueous dispersion at 25°C.

[a] Results of laboratory project for third edition.

11. Stability and Storage Conditions

Pregelatinized starch is a stable, though hygroscopic material, which should be stored in a well-closed container in a cool, dry, place.

12. Incompatibilities

–

13. Method of Manufacture

Food-grade pregelatinized starches are prepared by heating an aqueous slurry containing up to 42% w/w of starch at 62-72°C. Chemical additives which may be included in the slurry are gelatinization aids (salts or bases) and surfactants, added to control rehydration or minimize stickiness during drying. After heating, the slurry may be spray-dried, roll-dried, extruded, or drum-dried. In the latter case, the dried material may be processed to produce a desired particle size range.

Pharmaceutical grades of fully pregelatinized starch use no additives and are prepared by spreading an aqueous suspension of ungelatinized starch on hot drums where gelatinization and subsequent drying takes place. Partially pregelatinized starch is produced by subjecting moistened starch to mechanical pressure. The resultant material is ground and the moisture content adjusted to specifications.

14. Safety

Pregelatinized starch and starch are widely used in oral solid-dosage formulations. Pregelatinized starch is generally regarded as a nontoxic and nonirritant excipient. However, oral consumption of massive amounts of pregelatinized starch may be harmful.

See Starch for further information.

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and a dust mask are recommended. Excessive dust generation should be avoided to minimize the risks of explosions.

In the UK, the long-term (8-hour TWA) occupational exposure limits for starch are, 10 mg/m^3 for total inhalable dust and 5 mg/m^3 for respirable dust.[17]

16. Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral capsules, suspensions, and tablets). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Eur and US.

18. Related Substances

Starch; starch, sterilizable maize.

19. Comments

A low moisture grade of pregelatinized starch, *Starch 1500 L.M.* (Colorcon), containing less than 7% of water, specifically intended for use as a diluent in capsule formulations is commercially available.[12]

Sepistab ST 200 is described as an agglomerate of starch granules consisting of native and pregelatinized corn starch.[18]

20. Specific References

1. Small LE, Augsburger LL. Aspects of the lubrication requirements for an automatic capsule filling machine. *Drug Dev Ind Pharm* 1978; 4: 345-372.
2. Rudnic EM, Rhodes CT, Welch S, Bernardo P. Evaluations of the mechanism of disintegrant action. *Drug Dev Ind Pharm* 1982; 8: 87-109.
3. Manudhane KS, Contractor AM, Kim HY, Shangraw RF. Tableting properties of a directly compressible starch. *J Pharm Sci* 1969; 58: 616-620.
4. Underwood TW, Cadwallader DE. Influence of various starches on dissolution rate of salicylic acid from tablets. *J Pharm Sci* 1972; 61: 239-243.
5. Bolhuis GK, Lerk CF. Comparative evaluation of excipients for direct compression. *Pharm Weekbl* 1973; 108: 469-481.
6. Sakr AM, Elsabbagh HM, Emara KM. Sta-Rx 1500 starch: a new vehicle for the direct compression of tablets. *Arch Pharm* Chemi (Sci) 1974; 2: 14-24.
7. Schwartz JB, Martin ET, Dehner EJ. Intragranular starch: comparison of starch USP and modified cornstarch. *J Pharm Sci* 1975; 64: 328-332.
8. Rees JE, Rue PJ. Work required to cause failure of tablets in diametral compression. *Drug Dev Ind Pharm* 1978; 4: 131-156.

9. Shangraw RF, Wallace JW, Bowers FM. Morphology and functionality in tablet excipients for direct compression: part II. *Pharmaceut Technol* 1981; 5(10): 44-60.
10. Chilamkurti RW, Rhodes CT, Schwartz JB. Some studies on compression properties of tablet matrices using a computerized instrumental press. *Drug Dev Ind Pharm* 1982; 8: 63-86.
11. Malamataris S, Goidas P, Dimitriou A. Moisture sorption and tensile strength of some tableted direct compression excipients. *Int J Pharmaceutics* 1991; 68: 51-60.
12. Colorcon. Technical literature: *Starch 1500*, 1997.
13. Jaiyeoba KT, Spring MS. The granulation of ternary mixtures: the effect of the stability of the excipients. *J Pharm Pharmacol* 1980; 32: 1-5.
14. Carr RL. Particle behaviour storage and flow. *Br Chem Eng* 1970; 15: 1541-1549.
15. Callahan JC, Cleary GW, Elefant M, Kaplan G, Kensler T, Nash RA. Equilibrium moisture content of pharmaceutical excipients. *Drug Dev Ind Pharm* 1982; 8: 355-369.
16. Wurster DE, Peck GE, Kildsig DO. A comparison of the moisture adsorption-desorption properties of corn starch, U.S.P., and directly compressible starch. *Drug Dev Ind Pharm* 1982; 8: 343-354.
17. Health and Safety Executive. *EH40/98: Occupational Exposure Limits 1998*. Sudbury, Health and Safety Executive, 1998.
18. Seppic. Technical Literature: *Sepistab ST 200*, 1997.

21. General References

Monedeero Perales MC, Munoz-Ruiz A, Velasco-Antequera MV, Munoz Munoz N, and Jimenez-Castellanos Ballesteros MR. Comparative tableting and microstructural properties of a new starch for direct compression. *Drug Dev Ind Pharm* 1996; 22: 689-695.

Rees, JH and Tsardaka KD. Some effects of moisture on the viscoelastic behavior of modified starch during powder compaction. *Eur J Phar Biopharm* 1994; 40: 193-197.

Roquette Frères. Technical literature: *Lycatab PGS*, 1997.

Sanghvi PP, Collins CC, Shukla AJ. Evaluation of Prefio modified starches as new direct compression excipients I: tableting characteristics. *Pharm Res* 1993; 10: 1597-1603.

22. Authors

NG Lordi, G Rowley.